CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450..

Anastasia P. Winslow		October 27, 2005
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
LEE
APPLICATION NO: **10/091,061**
FILED: **MARCH 5, 2002**
FOR: **COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLIFERATIVE DISEASES**

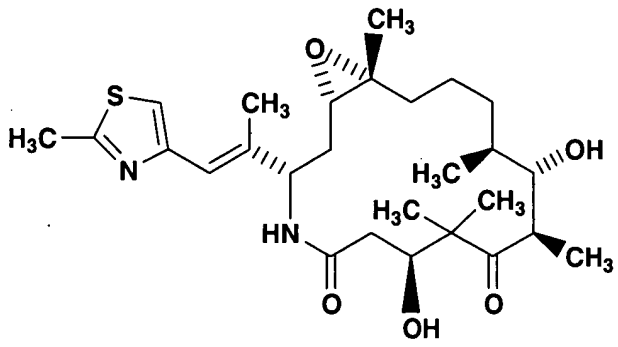
Art Unit: **1617**
Examiner: JIANG, SHAOJIA A

DECLARATION OF FRANCIS LEE

1. I am a Ph.D. research scientist employed with Bristol-Myers Squibb Company, in Princeton, New Jersey.

2. I have thirteen years of full-time experience in the pharmaceutical industry, including experience with preclinical models and evaluating compounds for oncological use based on preclinical *in vitro* and *in vivo* studies.

3. My work at BMS has involved preclinical studies related the aza-epothilone B analog, ixabepilone, which has the chemical structure:

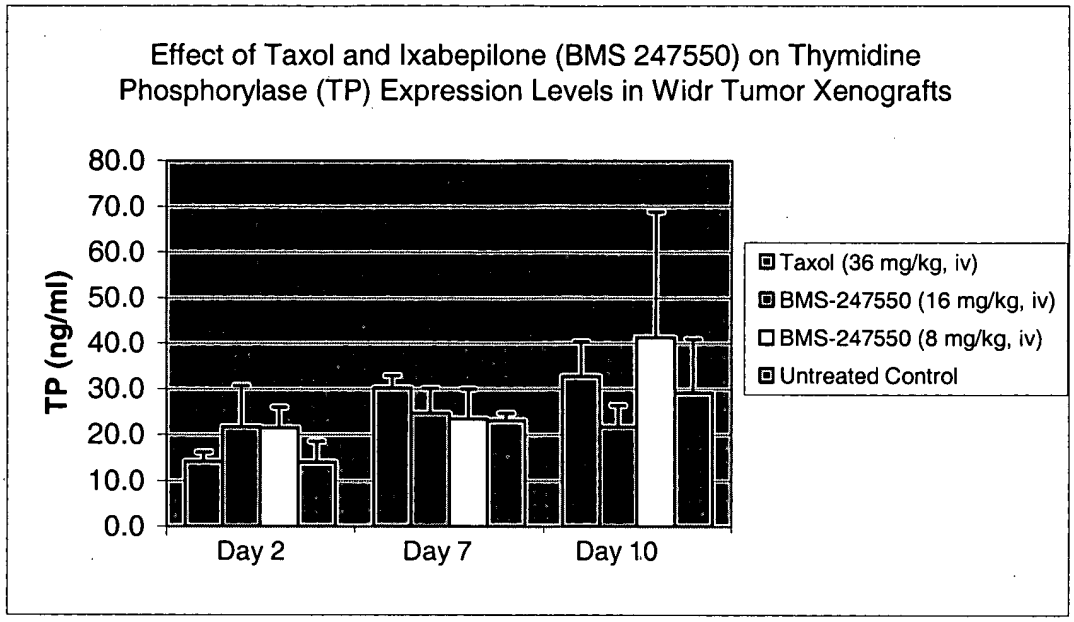


4. I am a named inventor on the instant patent application which claims combinations of ixabepilone and capecitabine. I make this Declaration in support of the patent claims to this combination of agents.

5. In 1998, a journal article was published by Sawada *et al.*, "*Induction of Thymidine Phosphorylase Activity and Enhancement of Capecitabine Efficacy by Taxol/Taxotere in Human Cancer Xenografts*," Clinical Cancer Research, Vol. 4, pp. 1013-1019, April 1998. This article reported that Taxol, Taxotere, and mitomycin C greatly increased levels of human thymidine Phosphorylase (TPs), in a WiDr human colon carcinoma xenograft tumor model (p. 1013). The TPs enzyme is known to be essential in triggering the conversion of the prodrug, capecitabine, to its active form, 5 fluorouracil. In this article, the authors reported that capecitabine is greatly modulated by TPs and that Taxol and Taxotere might enhance the efficacy of capecitabine by upregulating TPs (p. 1016). However, the authors reported that "the toxicity of Taxol/Taxotere and capecitabine does not appear to be synergistic, although the efficacy of these compounds in combination was additive to synergistic" (p. 1018).

6. Following review of this journal article, studies were performed to evaluate the effect of Taxol and ixabepilone on the induction of TPs levels in the WiDr human colon carcinoma xenograft model. In particular, a test was performed in which WiDr tumors were implanted subcutaneously using tumor fragments obtained from donor mice. The tumors were allowed to grow to a pre-determined size of 150-300 mg. The animals were then evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight on a mg/kg basis. Taxol was administered at the efficacious dose of 36 mg/kg/inj (daily, via intravenous injection [IV]) and ixabepilone (BMS-247550) was administered at dose levels of 16 and 8 mg/kg/inj (daily, via IV). Tumors (3 samples per treatment group and time point) were then harvested on day 2, day 7, and day 10-post drug administration and the relative level of TP in each sample was determined.

7. Results of the above-referenced study are set forth below. As can be seen in the below figure, it was determined that Taxol showed a slight increase in TP levels compared to untreated control on day 7 post-treatment (1.31-fold increase versus untreated control, $p < 0.05$). However, on day 2 or day 10 post-treatment, TP levels were indistinguishable from untreated control. Ixabepilone (BMS 247550), at both dose levels failed to significantly increase TP level over untreated controls on either day 2, day 7, or day 10.



8. From the above results, I expected that ixabepilone would *not* have a synergistic effect in combination with capecitabine in preclinical tumor cell models. This expectation stemmed from the fact that TP is essential to trigger the conversion of capecitabine to 5-FU, and the studies demonstrated that ixabepilone failed to significantly increase TP levels in the above-referenced xenograft tumor model.

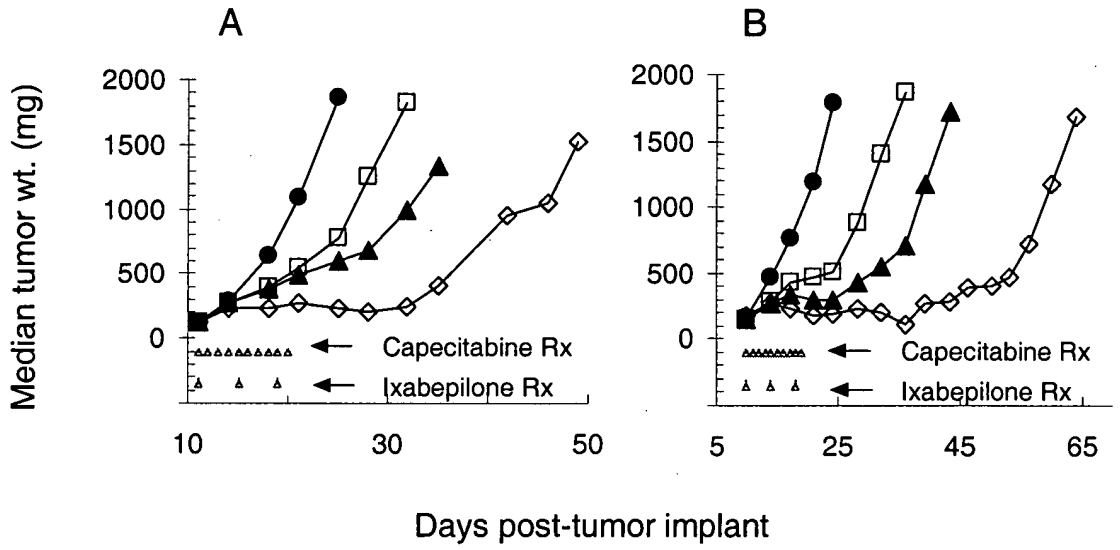
9. Contrary to my expectation and surprisingly, I discovered a synergistic effect is obtained in preclinical studies involving the administration of ixabepilone and capecitabine in combination.

10. For example, despite the results obtained from the TP up-regulation study, discussed above, the human colon carcinoma cell line GEO was used to evaluate the combined efficacy of ixabepilone and capecitabine in two repeated studies. In these two studies, human tumors were

propagated as subcutaneous transplants in an appropriate mouse strain using tumor fragments obtained from donor mice. In one study, single agent ixabepilone alone was administered to one group of tumor-implanted mice at its maximum tolerated dose (MTD) of 10 mg/kg, via an intravenous injection (IV), three times once every four days (Q4D x 3). In a second group of tumor-implanted mice, capecitabine alone was administered at its MTD, namely, 250 mg/kg/adm, administered orally (PO) once every (Q) day (D) for ten consecutive days (QD x 10). In a third group of mice, the two agents were administered together, *i.e.*, capecitabine at 250 mg/kg/adm, QD x 10 (orally) in combination with ixabepilone at 10 mg/kg/adm., Q4D x 3 (via IV). The tumor growth during the course of administration was measured and compared with tumor growth of a control group of mice, receiving tumor implants and no chemotherapeutic treatment. From the studies, it was determined that combination of the two agents surprisingly produced preclinical therapeutic synergism, yielding anti-tumor efficacy that was superior to either of the single agents alone at their MTDs. Similar results were obtained in an independent confirmatory study.

12. More specifically, the two graphs below represent results that were obtained from the two independent studies comparing the effects of monotherapy involving either ixabepilone or capecitabine, as compared with a combination therapy involving these two agents together. In these figures, each symbol represents the median tumor burden of a group of 8 mice. The symbol (●) represents results from the control group; the symbol (□) represents results from the capecitabine alone group (250 mg/kg/adm, QD x 10, PO); the symbol (▲) represents results

from the ixabepilone alone group (10 mg/kg/adm, Q4D x 3, IV); and lastly, the symbol (◇) represents the results achieved with the mice receiving the combination therapy of capecitabine (250 mg/kg/adm, QD x 10, PO), and ixabepilone (10 mg/kg/adm, Q4D x 3, IV). When administered on the same day, the two agents were given more or less simultaneously (ixabepilone preceded capecitabine by less than 1 hr).



13. The below table provides the results from the two studies in numerical form wherein the term "MTD" refers to the maximum tolerated dose, the letter "Q" means daily, the term "PO" means orally administered, and "LCK" refers to "gross log 10 cell kill", which is a measure of tumor response (tumor cell kill).

Antitumor efficacy of Combined Chemotherapy with Ixabepilone and Capecitabine Versus the GEO Human Colon Carcinoma

	Treatment		Efficacy/Toxicity			
	Ixabepilone Dose[a,b]	Capecitabine Dose[a,c]	Tumor Growth Delay[d]		Wt. Change	
Study	(mg/kg)	(mg/kg)	(LCK)	(days)	(g)	P[e]
No. 1	10	-	0.8	11	-3.8	0.035
	-	250	0.4	5.5	0.2	0.0004
	10	250	1.9	25.2	-4.9	-
No. 2	10	-	1.2	18.7	-4.2	0.0037
	-	250	0.6	9.7	-0.3	0.0038
	10	250	3.9	62	-4.2	-

[a] MTD; [b] Regimen: = IV, Q4D x 3; [c] Regimen: = PO, QD x 10; [d] Target tumor size = 1000 mg;
[e] P value is for comparison with the combination group

14. As can be seen from the above graphs and tabulated data, the delay in tumor growth when ixabepilone and capecitabine were administered in combination was more than additive as compared with monotherapy involving either agent alone. For example, in Study No. 1, anti-tumor efficacy obtained with the combination (LCK = 1.9) was greater than that achieved with either agent alone, even when the monotherapy effects are combined (0.8 + 0.4), and the period of growth delay was also more than additive for the combination (*i.e.*, delay of 25.2 days for the combination therapy, as compared with delay of 11 + 5.5 days for the combined single agent therapies.) In Study No. 2, again, anti-tumor efficacy obtained with the combination (LCK = 3.9) was greater than that achieved with either agent alone, even when the monotherapy effects are combined (1.2 + 0.6), and the period of growth delay was also more than additive for the

combination (*i.e.*, delay of 62 days for the combination therapy, as compared with 18.7 +9.7 days for the combined single agent therapy.)

15. In my opinion, the above studies demonstrated a synergistic effect is obtained in preclinical studies involving the administration of ixabepilone and capecitabine, in combination, and I found this synergistic effect to be surprising, particularly given our previous study which demonstrated that ixabepilone did not upregulate TPs.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant Application or any patent issuing therefrom.

Dated: 10/26/2005
(Month/Day/Year)

Francis Lee